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WO 96/24348 (15.08.1996 Gazette 1996/37)(54) USE OF CARBAZOLE COMPOUNDS FOR THE MANUFACTURE OF A MEDICAMENT FOR THE
TREATMENT OF CONGESTIVE HEART FAILUREVERWENDUNG VON CARBAZOLVERBINDUNGEN ZUR HERSTELLUNG EINES ARZNEIMITTELS
FÜR DIE BEHANDLUNG VON KONGESTIVEM HERZVERSGENUTILISATION DE COMPOSES DE CARBAZOLE POUR LA MANUFACTURE D'UN MEDICAMENT
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carvedilol on ventricular arrhythmias."

Description**Field of the Invention**

5 [0001] The present invention relates to a new method of treatment using compounds which are dual non-selective β -adrenoceptor and α_1 -adrenoceptor antagonists, in particular the carbazolyl-(4)-oxypropanolamine compounds of Formula I, preferably carvedilol, for decreasing the mortality of patients suffering from congestive heart failure (CHF). The invention also relates to a method of treatment using compounds which are dual non-selective β -adrenoceptor and α_1 -adrenoceptor antagonists in particular the carbazolyl-(4)-oxypropanolamine compounds of Formula I, preferably 10 carvedilol, in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of angiotensin converting enzyme (ACE) inhibitors, diuretics, and cardiac glycosides, for decreasing the mortality of patients suffering from CHF. The invention further relates to an incremental application scheme for administering compounds which are β -adrenoreceptor and α_1 -adrenoreceptor antagonists.

15 Background of the Invention

[0002] Congestive heart failure occurs as a result of impaired pumping capability of the heart and is associated with abnormal retention of water and sodium. Traditionally, treatment of chronic mild failure has included limitation of physical activity, restriction of salt intake, and the use of a diuretic. If these measures are not sufficient, a cardiac glycoside, 20 which is an agent that increases the force of myocardial contraction, is typically added to the treatment regimen.

[0003] Subsequently, angiotensin converting enzyme inhibitors, which are compounds that prevent the conversion of angiotensin I into the pressor-active angiotensin II, are prescribed for chronic treatment of congestive heart failure, in conjunction with a diuretic, a cardiac glycoside, or both.

[0004] Also, congestive heart failure is a well-known cardiac disorder which results in an excess mortality. Applefeld, 25 M.M., (1986) Am. J. Med., 80, Suppl. 2B, 73-77. Therefore, therapeutic agents that would decrease the mortality resulting from CHF in patients suffering therefrom are highly desirable.

[0005] J. Cardiovasc. pharmacol. 1992, 19 suppl. 1 PS62-7, Das Gupta p: et Al. "Can intravenous beta-blockade predict long-term hemodynamic benefit in chronic congestive heart failure secondary to ischemic heart disease? A comparison with oral carvedilol." concerns first investigations with carvedilol and shows some positive effects on haemodynamics and symptoms.

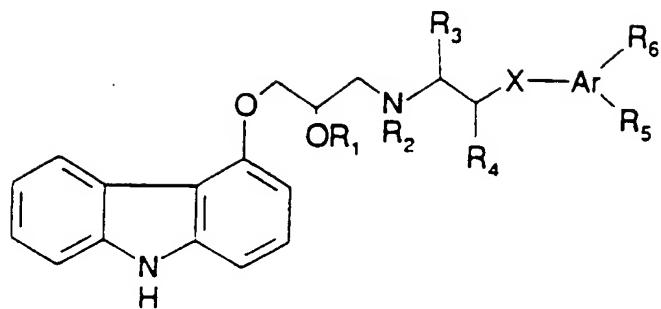
[0006] J. Cardiovasc. pharmacol. 1992, 19 suppl. 1 PS117-21, Senior R et Al. "Effects of carvedilol on ventricular arrhythmias" relates to the beneficial effects of carvedilol on left ventricular function in a group of patients with congestive heart failure and exclusively deals with influence of carvedilol on arrhythmias in various cardiovascular disorders.

35 Summary of the Invention

[0007] The present invention provides a new use of compounds which are dual non-selective β -adrenoceptor and α_1 -adrenoceptor antagonists for the preparation of medicaments for the treatment of congestive heart failure. In particular, the carbazolyl-(4)-oxypropanol-amine compounds of Formula I are preferred alone or in conjunction with one or more 40 other therapeutic agents, said agents being selected from the group consisting of ACE inhibitors, diuretics, and cardiac glycosides, as therapeutics for decreasing mortality resulting from congestive heart failure in mammals, particular. In particular, the present invention preferably provides a method of treatment, alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of ACE inhibitors, diuretics, and cardiac glycosides, for the compound of Formula I wherein R₁ is -H, R₂ is -H, R₃ is -H, R₄ is -H, X is 0, Ar is phenyl, R₅ is ortho 45 -OCH₃, and R₆ is -H, said compound being better known as carvedilol, which is (1-(carbazol-4-yloxy-3-[(2-(2-methoxyphenoxy) ethyl]amino]2-propanol), or a pharmaceutically acceptable salt thereof.

Detailed Description of the Invention

50 [0008] U.S. Pat. No. 4,503,067 discloses carbazolyl-(4)-oxypropanolamine compounds of Formula I:



wherein

20 R₁ is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

R₂ is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

25 R₃ is hydrogen or lower alkyl of up to 6 carbon atoms;

R₄ is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R₄ together with R₅ can represent -CH₂-O-;

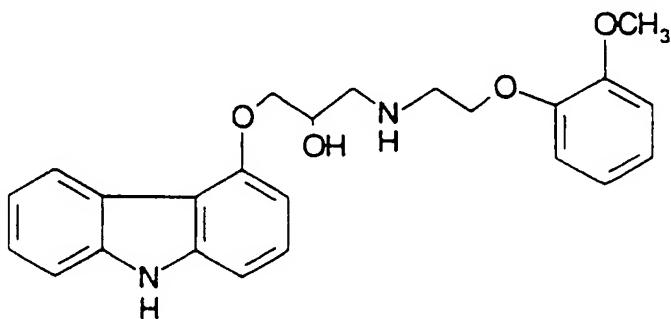
30 X is a valency bond, -CH₂, oxygen or sulfur;

Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl;

35 R₅ and R₆ are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a -CONH₂- group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkysulphonyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R₅ and R₆ together represent methylenedioxy; and pharmaceutically acceptable salts thereof.

40 [0009] This patent further discloses a compound of Formula I, better known as carvedilol, which is (1-(carbazol-4-yl oxy-3-[[2-(2-methoxyphenoxy)ethyl]amino](2-propanol), having the structure shown in Formula II:



Formula I compounds, of which carvedilol is exemplary, are novel multiple action drugs useful in the treatment of mild to moderate hypertension. Carvedilol is known to be both a competitive non-selective β -adrenoceptor antagonist and a vasodilator, and is also a calcium channel antagonist at higher concentrations. The vasodilatory actions of carvedilol result primarily from α_1 -adrenoceptor blockade, whereas the β -adrenoceptor blocking activity of the drug prevents reflex tachycardia when used in the treatment of hypertension. These multiple actions of carvedilol are responsible for the antihypertensive efficacy of the drug in animals, particularly in humans. See Willette, R.N., Sauermelch, C.F. & Ruffolo, R.R., Jr. (1990) *Eur. J. Pharmacol.*, **176**, 237-240; Nichols, A.J., Gellai, M. & Ruffolo, R.R., Jr. (1991) *Fundam. Clin. Pharmacol.*, **5**, 25-38; Ruffolo, R.R., Jr., Gellai, M., Hieble, J.P., Willette, R.N. & Nichols, A.J. (1990) *Eur. J. Clin. Pharmacol.*, **38**, S82-588; Ruffolo, R.R., Jr., Boyle, D.A., Venuti, R.P. & Lukas, M.A. (1991) *Drugs of Today*, **27**, 465-492; and Yue, T.-L., Cheng, H., Lysko, P.G., McKenna, P.J., Feuerstein, R., Gu, I., Lysko, K.A., Davis, L.L. & Feuerstein, G. (1992) *J. Pharmacol. Exp. Ther.*, **263**, 92-98.

[0010] The antihypertensive action of carvedilol is mediated primarily by decreasing total peripheral vascular resistance without causing the concomitant reflex changes in heart rate commonly associated with other antihypertensive agents. Willette, R.N., et al. *supra*; Nichols, A.J., et al. *supra*; Ruffolo, R.R., Jr., Gellai, M., Hieble, J.P., Willette, R.N. & Nichols, A.J. (1990) *Eur. J. Clin. Pharmacol.*, **38**, S82-S88. Carvedilol also markedly reduces infarct size in rat, canine and porcine models of acute myocardial infarction, Ruffolo, R.R., Jr., et al., *Drugs of Today*, *supra*, possibly as a consequence of its antioxidant action in attenuating oxygen free radical-initiated lipid peroxidation. Yue, T.-L., et al. *supra*.

[0011] Recently, it has been discovered in clinical studies that pharmaceutical compounds which are dual non-selective β -adrenoceptor and α_1 -adrenoceptor antagonists, in particular the compounds of Formula I, preferably carvedilol, alone or in conjunction with conventional agents, said agents being ACE inhibitors, diuretics, and cardiac glycosides, are effective therapeutic agents for treating CHF. The use of agents, such as carvedilol in treating CHF is surprising, since, in general, β -blockers are contraindicated in patients suffering from heart failure, because β -blockers are known to have undesirable cardiodepressive effects. The most surprising observation from the studies in which the instant compounds were used to treat CHF is that said compounds, in particular carvedilol, are able to decrease the mortality resulting from CHF in humans by about 67 percent. Furthermore, this result is present across all classifications of CHF and both etiologies (eschemic and non-eschemic). This result is surprising since two recent mortality studies using the β -blockers metoprolol (Waagstein, et al., (1993) *Lancet*, **342**, 1441-1446) and bisoprolol (CIBIS investigators and committees, (1994) *Circulation*, **90**, 1765-1773) in the treatment of CHF showed no difference in mortality between drug-treated patients and placebo-treated patients.

[0012] According to the method of treatment of the present invention, the desirable therapeutic effect of the compounds of Formula I, particularly carvedilol, may be augmented by using any one of said compounds; or any pharmaceutically acceptable salt of said compounds, in conjunction with ACE inhibitors, diuretics, and cardiac glycosides, which are effective therapeutic agents for the treatment of CHF. In particular, the preferred ACE inhibitors of the present invention are selected from the group consisting of captopril, lisinopril, fosinopril and enalapril, or any pharmaceutically acceptable salts thereof and the preferred diuretics of the present invention are hydrochlorothiazide furosemide, or torasemide or any pharmaceutically acceptable salts thereof. The preferred cardiac glycosides of the present invention are digoxin, β -methyldigoxin or digitoxin. The desirable therapeutic benefits of the compounds of Formula I, particularly carvedilol, are additive with those of such ACE inhibitors, or diuretics, or cardiac glycosides when administered in combination therewith. Captopril is commercially available from E.R. Squibb & Sons, Inc. Lisinopril, enalapril and hydrochlorothiazide are commercially available from Merck & Co. Furosemide is commercially available from Hoechst-Roussel Pharmaceuticals, Inc. Digoxin is commercially available from Burroughs Wellcome Co. and Boehringer Mannheim GmbH. Digitoxin, β -Methyldigoxin, fosinopril and torasemide are commercially available from Boehringer Mannheim GmbH.

[0013] Compounds of Formula I may be conveniently prepared as described in U.S. Pat. No. 4,503,067. Carvedilol is commercially available from SmithKline Beecham Corporation and Boehringer Mannheim GmbH (Germany).

[0014] Pharmaceutical compositions of the compounds of Formula I, including carvedilol, alone or in combination with ACE inhibitors, or diuretics, or cardiac glycosides may be administered to patients according to the present invention in any medically acceptable manner, preferably orally. For parenteral administration, the pharmaceutical composition will be in the form of a sterile injectable liquid stored in a suitable container such as an ampoule, or in the form of an aqueous or nonaqueous liquid suspension. The nature and composition of the pharmaceutical carrier, diluent or excipient will, of course, depend on the intended route of administration, for example whether by intravenous or intramuscular injection.

[0015] Pharmaceutical compositions of the compounds of Formula I for use according to the present invention may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation is generally a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or neb-

ulizer for insufflation. It may be desirable to add excipients such as ethanol, polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

[0016] Alternatively, these compounds may be encapsulated, tableted or prepared in an emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Liquid carriers include syrup, peanut oil, olive oil, glycerin, saline, ethanol, and water. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension.

[0017] Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

[0018] Compounds having the above-mentioned dual properties are preferably administered following a three-stage application scheme. This scheme is characterized by the fact that incremental dosages of the active ingredient are administered to patients over a certain period of time, until the regular maintenance dosage is received. If this maintenance dosage is defined as the setting value being 100 %, it was found that the application regimen in a first phase should extend for a period of 7 - 28 days, whereby only 10-30 % of the setting dose are administered. Following this phase, a second application regimen should follow, wherein a dosage of 20 - 70 % of the setting dose is administered to the patient for a period of 7 - 28 days. After termination of this phase, the third application period follows, wherein the daily complete setting dose (maintenance dose) is administered. The daily maintenance dose can vary between 10 - 100 mg of said active ingredient.

[0019] In case of carvedilol, dosing in humans for the treatment of disease according to the present invention should not exceed a dosage range of from about 3.125 to about 50 mg of the compounds of Formula I, particularly carvedilol, preferably given twice daily. As one of ordinary skill in the art will readily comprehend, the patient should be started on a low dosage regimen of the desired compound of Formula I, particularly carvedilol, and monitored for well-known symptoms of intolerance, e.g., fainting, to such compound. Once the patient is found to tolerate such compound, the patient should be brought slowly and incrementally up to the maintenance dose. The preferred course of treatment is to start the patient on a dosage regimen with formulations which contain either 3.125 or 6.25 mg of active compound per single unit, preferably given twice daily, for 7 - 28 days. The choice of initial dosage most appropriate for the particular patient is determined by the practitioner using well-known medical principles, including, but not limited to, body weight. In the event that the patient exhibits medically acceptable tolerance of the compound for two weeks, the dosage is doubled at the end of the two weeks and the patient is maintained at the new, higher dosage for an additional period, preferably to two more weeks, and observed for signs of intolerance. This course is continued until the patient is brought to a maintenance dose. The preferred maintenance dose is 25.0 mg of active compound per single unit, preferably given twice daily, for patients having a body weight of up to 85 kg. For patients having a body weight of over 85 kg, the maintenance dose is between about 25.0 mg and about 50.0 mg, preferably given twice daily; preferably about 50.0 mg of active compound per single unit, preferably given twice daily.

[0020] The present invention relates also to method of treatment for decreasing mortality resulting from congestive heart failure in mammals comprising internally administering to said mammal in need thereof an effective amount of carvedilol according to the following schedule:

(a) a pharmaceutical formulation which contains either 3.125 or 6.25 mg carvedilol per single unit for a period of 7 - 28 days, given once or twice daily,

(b) thereafter a pharmaceutical formulation which contains 12.5 mg carvedilol per single unit for a period of additional 7 - 28 days, given once or twice daily, and

(c) finally a pharmaceutical formulation which contains either 25.0 or 50.0 mg carvedilol per single unit, given once or twice daily as a maintenance dose.

[0021] Dosing in humans for the treatment of disease according to the present invention includes the combination of compounds of Formula I with conventional agents. For example, the usual adult dosage of hydrochlorothiazide is 25 - 100 mg daily as a single dose or divided dose. The recommended starting dose for enalapril is 2.5 mg administered once or twice daily. The usual therapeutic dosing range for enalapril is 5 - 20 mg daily, given as a single dose or two divided doses. For most patients the usual initial daily dosage of captopril is 25 mg three times per day (tid), with most patients having a satisfactory clinical improvement at 50 or 100 mg three times per day (tid).

[0022] It will be appreciated that the actual preferred dosages of the compounds being used in the compositions of

this invention will vary according to the particular composition formulated, the mode of administration, the particular site of administration and the host being treated.

[0023] No unacceptable toxicological effects are expected when the compounds of Formula I, including the compound of Formula II, are used according to the present invention. The example which follows is intended in no way to limit the scope of this invention, but is provided to illustrate how to use the compounds of this invention. Many other embodiments will be readily apparent to those skilled in the art.

Experimental

10 Mortality Studies in CHF Patients

[0024] **Summary.** To determine if β -adrenergic blockade might inhibit the deleterious effects of the sympathetic nervous system on survival in heart failure (CHF), 1052 patients with CHF were prospectively enrolled into a multicenter trial program, in which patients were randomly assigned (double-blind) to 6-12 months' treatment with placebo (PBO) or carvedilol (CRV). After a common screening period, patients with class II-IV CHF (see next paragraph for the definitions of the classification of CI) and an ejection fraction < 0.35 were assigned to one of four protocols based on performance on a 6-minute walk test. PBO or CRV was added to existing therapy with digoxin, diuretics and an ACE inhibitor. All-cause mortality was monitored by a prospectively constituted Data and Safety Monitoring Board (DSMB). After 25 months of enrollment, the DSMB recommended termination of the program because of a favorable effect of CRV on survival. By intention-to-treat, mortality was 8.2% in the PBO group but only 2.9% in the CRV group ($P = 0.0001$, Cochran-Mantel-Haensel analysis). This represented a reduction in risk of death by CRV of 67% (95% CI: 42% to 81%). The treatment effect was similar in patients with class II and class III-IV symptoms. Mortality was reduced in class II patients from 5.9% to 1.9%, a 68% reduction (95% CI: 20% to 97%) [$P = 0.015$], and in class III-IV patients from 11.0% to 4.2%, a 67% reduction (95% CI: 30% to 84%), [$P = 0.004$, log-rank]. Importantly, the effect of CRV was similar in ischemic heart disease (risk reduced by 67%, $P = 0.003$) and in nonischemic dilated cardiomyopathy (risk reduced by 67%, $P = 0.014$). In conclusion, the addition of CRV to conventional therapy is associated with a substantial (67%) reduction in the mortality of patients with chronic CHF. The treatment effect is seen across a broad range of severity and etiology of disease.

[0025] As used herein, by "Class II CHF" is meant patients with cardiac disease resulting in slight or moderate limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain. By "Class III CHF" is meant patients with cardiac disease resulting in marked limitations of physical activity. They are comfortable at rest. Less than ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain. By "Class IV CI" is meant patients with cardiac disease resulting in inability to carry on any physical activity without discomfort, symptoms or cardiac insufficiency, or of the anginal syndrome. By "less than ordinary physical activity" is meant climbing one flight of stairs, or walking two hundred yards

[0026] **Design of Study.** Patients on background therapy with diuretics, ACE inhibitors and/or digoxin were stratified on the basis of baseline submaximal exercise performance, into one of four trials:

- study 220, a dose response study in moderate (NYHA II-IV) CHF with exercise testing as a primary endpoint
- study 221, a dose titration study in moderate (NYHA II-IV) CI with exercise testing as a primary endpoint
- study 239, a dose titration study in severe (NYHA III-IV) CHF with quality of life as a primary endpoint
- study 240, a dose titration study in mild (NYHA II-III) CHF with progression of CHF as a primary endpoint

[0027] Sixty-four centers in the US participated in the trial program. All sites conducted protocols 239 and 240, while 33 performed protocol 220 and 31 performed protocol 221.

[0028] Although each trial had its own individual objectives, the overall program objective defined prospectively was evaluation of all-cause mortality. Based upon a projected enrollment of 1100 patients, the program had 90% power to detect a 50% reduction in mortality (two-sided) between carvedilol and placebo, assuming a mortality rate in the placebo group of 12% over the duration of the trials ($\alpha = 0.05$).

[0029] Randomization was preceded by a screening and challenge period common to the four protocols. The purpose of the screening period was to qualify patients for study entry, obtain reproducible baseline measurements, and stratify patients into the appropriate trial based on submaximal exercise testing. During the challenge period, patients received low-dose open-label carvedilol (6.25 mg b.i.d.) for two weeks. Patients unable to tolerate this dose did not proceed to randomization. Patients tolerating low-dose carvedilol were then randomized to blinded medication (carvedilol or placebo) with the dose titrated over several weeks in the range of 6.25 to 50 mg b.i.d. (or equivalent level of placebo). The

5 maintenance phase of each study ranged from six to 12 months, after which patients had the option of receiving open-label carvedilol in an extension study.

10 [0030] **Results.** The analysis presented below corresponds to the data set on which the DSMB made the recommendation to terminate the trials. Included in this intent-to-eat analysis are all patients enrolled in the US trials as of January 20, 1995; 624 receiving carvedilol and 356 placebo. An analysis of baseline patient characteristics (Table 1) shows good balance between the randomized groups.

Table 1

| US Carvedilol Heart Failure Trials - Baseline Characteristics | | |
|---|-------------------|----------------------|
| Characteristic | Placebo (n = 356) | Carvedilol (n = 624) |
| Age, mean + SD (years) | 59.9+11.7 | 58.8+11.8 |
| Sex (% men) | 62% | 62% |
| Etiology (% ischemic) | 43% | 40% |
| Severity of CHF | | |
| Class II | 41% | 41% |
| Class III-IV | 40% | 39% |
| Unknown | 19% | 20% |
| LV ejection fraction, mean + SD | 0.22 + 0.07 | 0.23 + 0.08 |
| 6 Minute walk (m + SD) | 373+88 | 379+81 |
| Blood pressure (mmHg) | 115/73 | 115/73 |
| Heart rate (bpm + SD) | 85 ± 13 | 86 ± 13 |

15 [0031] The overall mortality results for the program are shown in Table 2. All deaths that occurred during the intent-to-treat period are included. Treatment with carvedilol resulted in a 67% reduction in the risk of all-cause mortality. Analysis of mortality by certain baseline characteristics shows this to be a broad effect regardless of severity or etiology of CHF. The effect was uniform in patients with mild heart failure or moderate to severe heart failure. Similarly, the mortality reduction was equivalent in patients with ischemic or non-ischemic heart failure.

20

Table 2

| Evaluation of Mortality in US Carvedilol CHF Studies | | | | |
|--|----------------|-----------------|--------------------------|----------|
| | Carvedilol | Placebo | Risk reduction (95 % CI) | p value* |
| All Cause Mortality | 18/624 (2.9 %) | 29/356 (8.2 %) | 67 % (42 - 81) | < 0.001 |
| Class II CHF | 7/361 (1.9 %) | 12/202 (5.9 %) | 68 % (20 - 97) | 0.015 |
| Class III-IV CHF | 11/263 (4.2 %) | 17/154 (11.0 %) | 66 % (30 - 84) | 0.004 |
| Ischemic Etiology | 10/311 (3.2 %) | 16/178 (8.9 %) | 67 % (32 - 85) | 0.003 |
| Non-Ischemic Etiology | 8/313 (2.5 %) | 13/178 (7.3 %) | 67 % (20 - 86) | 0.014 |

25 *Cochran-Mantel-Haensel Analysis

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35 [0032] The foregoing is illustrative of the use of the compounds of this invention.

40 Claims

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1. The use of a compound which is both a β -adrenoreceptor antagonist and a α_1 -adrenoreceptor antagonists for the manufacture of a medicament for decreasing mortality resulting from congestive heart failure in mammals, alone or in conjunction with one or more other therapeutic agents, said agents selected from the group consisting of an angi-

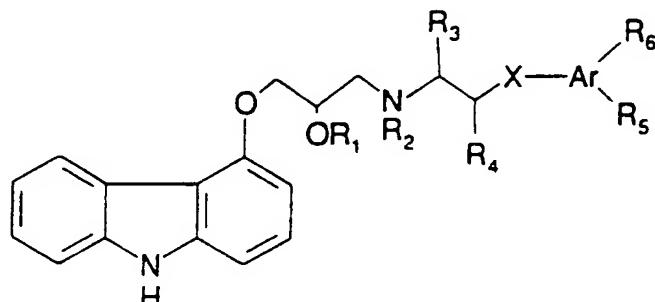
otensin converting enzyme inhibitor, a diuretic and a cardiac glycosides.

2. The use of a compound according to claim 1, wherein said compound is subject of formula I

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10

15



(I)

20

wherein

R₁ is hydrogen, lower alkanoyl of up to 6 carbon atoms or aroyl selected from benzoyl and naphthoyl;

25

R₂ is hydrogen, lower alkyl of up to 6 carbon atoms or arylalkyl selected from benzyl, phenylethyl and phenylpropyl;

R₃ is hydrogen or lower alkyl of up to 6 carbon atoms;

30

R₄ is hydrogen or lower alkyl of up to 6 carbon atoms, or when X is oxygen, R₄ together with R₅ can represent -CH₂-O-;

X is a valency bond, -CH₂, oxygen or sulfur;

35

Ar is selected from phenyl, naphthyl, indanyl and tetrahydronaphthyl;

40

R₅ and R₆ are individually selected from hydrogen, fluorine, chlorine, bromine, hydroxyl, lower alkyl of up to 6 carbon atoms, a -CONH₂- group, lower alkoxy of up to 6 carbon atoms, benzyloxy, lower alkylthio of up to 6 carbon atoms, lower alkylsulphonyl of up to 6 carbon atoms and lower alkylsulphonyl of up to 6 carbon atoms; or

R₅ and R₆ together represent methylenedioxy; and pharmaceutically acceptable salts thereof.

3. The use of a compound according to claim 1 or 2, wherein said compound is carvedilol.

45

4. The use of a compound according to claim 3, whereby a pharmaceutical formulation containing either 3.125 or 6.25 mg carvedilol in a single unit are administered for a period of 7 - 28 days, once or twice daily as an initial dose.

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5. The use of a compound according to claim 3, whereby a pharmaceutical formulation containing 12.5 mg carvedilol in a single unit are administered for a period of 7 - 28 days, once or twice daily.

6. The use of a compound according to claim 3, whereby a pharmaceutical formulation containing either 25.0 or 50.0 mg carvedilol in a single unit are administered once or twice as a maintenance dose.

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7. The use of a compound according to claim 1, wherein said ACE inhibitor is selected from the group consisting of captopril, lisinopril, fosinopril or enalapril, or any pharmaceutically acceptable salt thereof.

8. The use of a compound according to claim 1, wherein said diuretic is selected from the group consisting of hydro-

chlorothiazide, torasemide or furosemide, or any pharmaceutically acceptable salt thereof.

9. The use of a compound according to claim 1, wherein said cardiac glycoside is selected from the group consisting of digoxin, β -methyl-digoxin or digitoxin.

5 10. The use of carvedilol for the manufacture of a medicament for decreasing mortality resulting from congestive heart failure in mammals according to the following regimen:

10 (a) administering a pharmaceutical formulation which contains either 3.125 or 6.25 mg carvedilol per single unit for a period of 7 - 28 days, given once or twice daily,

15 (b) administering thereafter a pharmaceutical formulation which contains 12.5 mg carvedilol per single unit for a period of additional 7 - 28 days, given once or twice daily and

15 (c) administering finally a pharmaceutical formulation which contains either 25.0 or 50.0 mg carvedilol per single unit, given once or twice daily as a maintenance dose.

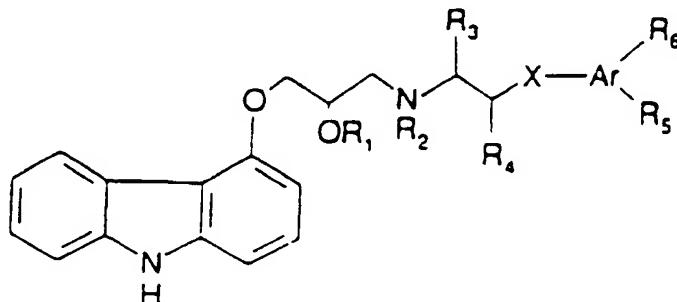
20 11. The use of carvedilol according to claim 10, whereby carvedilol is administered in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of an angiotensin converting enzyme inhibitor, a diuretic and a cardiac glycoside.

25 12. Use of a compound according to claim 1 for the preparation of a medicament for the treatment of CHF to be administered in a daily maintenance dose of 10 - 100 mg, said medicament being administered in incremental dosage schemes comprising three dose regimens, the first regimen comprising administering an amount of 10 - 30 % of the daily maintenance dose of the compound for a period of 7 - 28 days, the second regimen comprising administering an amount of 20 - 70 % of said daily dose for a period of 7 - 28 days and a third regimen comprising administering 100 % of said daily dose starting after termination of the second regimen.

Patentansprüche

30 1. Verwendung einer Verbindung, die sowohl ein β -Adrenorezeptorantagonist als auch ein α_1 -Adrenorezeptorantagonist ist, zur Herstellung eines Medikaments zur Senkung der Mortalität aufgrund kongestiven Herzversagens bei Säugern, allein oder in Verbindung mit einem oder mehreren anderen therapeutischen Mitteln, wobei diese Mittel ausgewählt sind aus der Gruppe bestehend aus einem Hemmer für Angiotensin umwandelndes Enzym, einem Diuretikum und einem Herzglycosid.

35 2. Verwendung einer Verbindung nach Anspruch 1, bei der es sich um eine Verbindung der Formel I handelt:



(I)

worin

55 R₁ Wasserstoff, Niederalkanoyl mit bis zu 6 Kohlenstoff-Atomen oder ein aus Benzoyl und Naphthoyl ausgewähltes Aroyl ist,

R₂ Wasserstoff, Niederalkyl mit bis zu 6 Kohlenstoff-Atomen oder ein aus Benzyl, Phenylethyl und Phenylpropyl ausgewähltes Arylalkyl ist,

| | |
|--------------------------------------|---|
| R ₃ | Wasserstoff oder Niederalkyl mit bis zu 6 Kohlenstoff-Atomen ist, |
| R ₄ | Wasserstoff oder Niederalkyl mit bis zu 6 Kohlenstoff-Atomen ist, oder wenn X Sauerstoff ist, R ₄ zusammen mit R ₅ -CH ₂ -O- bedeuten kann, |
| X | eine Valenzbindung, -CH ₂ , Sauerstoff oder Schwefel ist, |
| 5 Ar | ausgewählt ist aus Phenyl, Naphthyl, Indanyl und Tetrahydronaphthyl, |
| R ₅ und R ₆ | individuell ausgewählt sind aus Wasserstoff, Fluor, Chlor, Brom, Hydroxyl, Niederalkyl mit bis zu 6 Kohlenstoff-Atomen, einer -CONH ₂ -Gruppe, Niederalkoxy mit bis zu 6 Kohlenstoff-Atomen, Benzyloxy, Niederalkylthio mit bis zu 6 Kohlenstoff-Atomen, Niederalkylsulfonyl mit bis zu 6 Kohlenstoff-Atomen und Niederalkylsulfonyl mit bis zu 6 Kohlenstoff-Atomen, oder |
| 10 R ₅ und R ₆ | zusammen Methylendioxy bedeuten, und der pharmazeutisch annehmbaren Salze derselben. |

3. Verwendung einer Verbindung nach Anspruch 1 oder 2, wobei die Verbindung Carvedilol ist.
- 15 4. Verwendung einer Verbindung nach Anspruch 3, wobei eine pharmazeutische Formulierung, enthaltend entweder 3,125 oder 6,25 mg Carvedilol in einer Einzeleinheit, über einen Zeitraum von 7-28 Tagen einmal oder zweimal täglich als Anfangsdosis verabreicht werden.
- 20 5. Verwendung einer Verbindung nach Anspruch 3, wobei eine pharmazeutische Formulierung, enthaltend 12,5 mg Carvedilol in einer Einzeleinheit, über einen Zeitraum von 7-28 Tagen einmal oder zweimal täglich verabreicht werden.
- 25 6. Verwendung einer Verbindung nach Anspruch 3, wobei eine pharmazeutische Formulierung, enthaltend entweder 25,0 oder 50,0 mg Carvedilol in einer Einzeleinheit, einmal oder zweimal täglich als Erhaltungsdosis verabreicht werden.
- 30 7. Verwendung einer Verbindung nach Anspruch 1, wobei der ACE-Hemmer ausgewählt ist aus der Gruppe bestehend aus Captopril, Lisinopril, Fosinopril oder Enalapril oder irgendeinem pharmazeutisch annehmbaren Salz derselben.
8. Verwendung einer Verbindung nach Anspruch 1, wobei das Diuretikum ausgewählt ist aus der Gruppe bestehend aus Hydrochlorothiazid, Torasemid oder Furosemid oder irgendeinem pharmazeutisch annehmbaren Salz derselben.
- 35 9. Verwendung einer Verbindung nach Anspruch 1, wobei das Herzglycosid ausgewählt ist aus der Gruppe bestehend aus Digoxin, β -Methyldigoxin oder Digitoxin.
10. Verwendung von Carvedilol zur Herstellung eines Medikaments zur Senkung der Mortalität aufgrund kongestiven Herzversagens bei Säugern gemäß folgendem Schema:
 - 40 (a) Verabreichung einer pharmazeutischen Formulierung, die entweder 3,125 oder 6,25 mg Carvedilol pro Einzeleinheit enthält, die über einen Zeitraum von 7-28 Tagen einmal oder zweimal täglich gegeben werden;
 - (b) danach Verabreichung einer pharmazeutischen Formulierung, die 12,5 mg Carvedilol pro Einzeleinheit enthält, die über einen Zeitraum von weiteren 7-28 Tagen einmal oder zweimal täglich gegeben werden; und
 - 45 (c) schließlich Verabreichung einer pharmazeutischen Formulierung, die entweder 25,0 oder 50,0 mg Carvedilol pro Einzeleinheit enthält, die einmal oder zweimal täglich als Erhaltungsdosis gegeben werden.
11. Verwendung von Carvedilol nach Anspruch 10, wobei Carvedilol in Verbindung mit einem oder mehreren anderen therapeutischen Mitteln verabreicht wird, wobei diese Mittel ausgewählt sind aus der Gruppe bestehend aus einem Hemmer für Angiotensin umwandelndes Enzym, einem Diuretikum und einem Herzglycosid.
- 50 12. Verwendung einer Verbindung nach Anspruch 1 zur Herstellung eines Medikaments zur Behandlung von kongestivem Herzversagen, das in einer täglichen Erhaltungsdosis von 10-100 mg zu verabreichen ist, wobei das Medikament in inkrementalen Dosierungsschemata verabreicht wird, die drei Dosisschemata umfassen, wobei das erste Schema die Verabreichung einer Menge von 10 bis 30% der täglichen Erhaltungsdosis der Verbindung über einen Zeitraum von 7-28 Tagen umfaßt, das zweite Schema die Verabreichung einer Menge von 20-70% dieser täglichen Dosis über einen Zeitraum von 7-28 Tagen umfaßt, und das dritte Schema die Verabreichung von 100% dieser täglichen Dosis umfaßt, die nach Beendigung des zweiten Schemas beginnt.

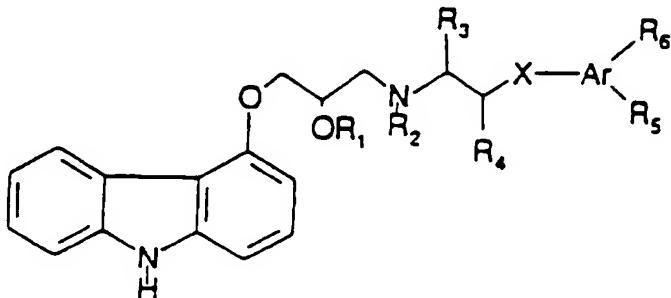
Revendications

5 1. Utilisation d'un composé qui est à la fois un antagoniste du β -adrénorécepteur et un antagoniste de l' α -adrénorécepteur pour la fabrication d'un médicament destiné à diminuer la mortalité résultant d'un infarctus congestif chez les mammifères, seul ou conjointement avec un ou plusieurs autres agents thérapeutiques, les lesdits agents choisis dans le groupe formé par un inhibiteur d'enzyme convertissant les angiotensines, un diurétique et des glycosides cardiaques.

10 2. Utilisation d'un composé selon la revendication 1, dans laquelle ledit composé est un sujet de formule 1

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dans laquelle

R₁ représente un atome d'hydrogène, un groupe alcanoyle inférieur ayant jusqu'à 6 atomes de carbone ou aroyle choisi parmi les groupes benzoyle et naphtoyle;

30 R₂ représente un atome d'hydrogène, un groupe alkyle inférieur ayant jusqu'à 6 atomes de carbone ou arylalkyle choisi parmi les groupes benzyle, phénylethyle et phénylpropyle;

R₃ représente un atome d'hydrogène ou un groupe alkyle inférieur ayant jusqu'à 6 atomes de carbone;

R₄ représente un atome d'hydrogène ou un groupe alkyle inférieur ayant jusqu'à 6 atomes de carbone ou, lorsque X est un atome d'oxygène, R₄ ensemble avec R₅ peuvent représenter -CH₂-O-;

35 X est une liaison de valence, -CH₂, un atome d'oxygène ou de soufre;

Ar est choisi parmi les groupes phényle, naphtyle, indanyle et tétrahydronaphtyle;

R₅ et R₆ sont choisis individuellement parmi un atome d'hydrogène, de fluor, de chlore, de brome, un groupe hydroxyle, alkyle inférieur ayant jusqu'à 6 atomes de carbone, un groupe -CONH₂-, alcoxy inférieur ayant jusqu'à 6 atomes de carbone, benzyloxy, alkylthio inférieur ayant jusqu'à 6 atomes de carbone, alkylsulfonyle inférieur ayant jusqu'à 6 atomes de carbone et alkylsulfonyle inférieur ayant jusqu'à 6 atomes de carbone; ou

40 R₅ et R₆ représentent ensemble un groupe méthylènedioxy; et leurs sels acceptables sur le plan pharmaceutique.

45 3. Utilisation d'un composé selon la revendication 1 ou 2, dans lequel ledit composé est le carvedilol.

50 4. Utilisation d'un composé selon la revendication 3, par laquelle une formulation pharmaceutique contenant 3,125 ou 6,25 mg de carvedilol dans une dose unitaire est administrée pendant une durée de 7 à 28 jours, une ou deux fois par jour comme dose initiale.

55 5. Utilisation d'un composé selon la revendication 3, par laquelle une formulation pharmaceutique contenant 12,5 mg de carvedilol dans une dose unitaire est administrée pendant une durée de 7 à 28 jours, une ou deux fois par jour.

6. Utilisation d'un composé selon la revendication 3, par laquelle une formulation pharmaceutique contenant 25,0 ou 50,0 mg de carvedilol en une dose unitaire est administrée une ou deux fois en tant que dose d'entretien.

55 7. Utilisation d'un composé selon la revendication 1, dans laquelle ledit inhibiteur ACE est choisi dans le groupe formé par captopril, lisinopril, fosinopril ou énalapril, ou un de leurs sels acceptables sur le plan pharmaceutique.

8. Utilisation d'un composé selon la revendication 1, dans laquelle ledit diurétique est choisi dans le groupe formé par l'hydrochlorothiazide, le torasémide ou le furosémide, ou un de leurs sels acceptables sur le plan pharmaceutique.
- 5 9. Utilisation d'un composé selon la revendication 1, dans laquelle ledit glycoside cardiaque est choisi dans le groupe formé par la digoxyne, la β -méthyl-digoxine ou la digitoxine.
- 10 10. Utilisation de carvedilol pour la fabrication d'un médicament destiné à diminuer la mortalité résultant d'un infarctus congestif chez les mammifères selon le régime suivant:
 - 10 (a) administration d'une formulation pharmaceutique qui contient 3,125 ou 6,25 mg de carvedilol par dose unitaire pendant une durée de 7 à 28 jours, donnée une ou deux fois par jour,
 - 10 (b) administration par la suite d'une formulation pharmaceutique qui contient 12,5 mg de carvedilol par dose unitaire pendant une période de 7 à 28 jours supplémentaires, donnée une ou deux fois par jour, et
 - 15 (c) administration finale d'une formulation pharmaceutique qui contient 25,0 ou 50,0 mg de carvedilol par dose unitaire, donnée une ou deux fois par jour en tant que dose de maintien.
11. Utilisation de carvedilol selon la revendication 10, par laquelle le carvedilol est administré conjointement avec un ou plusieurs autres agents thérapeutiques, lesdits agents étant choisis dans le groupe formé par un inhibiteur d'enzyme convertissant des angiotensines, un diurétique et un glycoside cardiaque.
- 20 12. Utilisation d'un composé selon la revendication 1 pour la préparation d'un médicament destiné au traitement de CHF à administrer à une dose d'entretien quotidienne de 10 à 100 mg, ledit médicament étant administré selon des schémas de dosage incrémentaux comprenant trois régimes de dose, le premier régime consistant à administrer une quantité de 10 à 30% de la dose d'entretien quotidienne du composé pendant une durée de 7 à 28 jours, le deuxième régime consistant à administrer une quantité de 20 à 70% de ladite dose quotidienne pendant une durée de 7 à 28 jours et un troisième régime consistant à administrer 100% de ladite dose quotidienne en commençant après avoir terminé le deuxième régime.
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